Variability in Flexible Sigmoidoscopy Performance Among Examiners in a Screening Trial

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Background & Aims: **The efficacy of flexible sigmoidoscopy (FSG) in reducing colorectal cancer mortality is being evaluated in randomized trials. In 2 European trials, wide variability across examiners in FSG performance was noted. We report on the performance of examiners in the US randomized trial: the Prostate, Lung, Colorectal and Ovarian Cancer Screening Trial.** **Methods:** **Screening was performed at 10 geographically dispersed clinical centers. Patients with screens positive for a lesion or mass were referred to their private health care providers for endoscopic follow-up evaluation; lesions were not removed and a biopsy examination was not performed at screening. FSG performance among 64 examiners at these centers, each performing 100 or more baseline FSG examinations, with an aggregate of almost 50,000 examinations, was analyzed.** **Results:** **Screen-positivity results among examiners ranged from 9%–58%, with a coefficient of variation (CV) of 36%. CVs were 29% for distal polyp detection and 21% for distal adenoma detection. Inadequate rates ranged from 1%–27% (CV, 52%). Examiners with higher screen-positivity rates had higher false-positive rates, defined as a positive screen with no distal lesion found on endoscopic follow-up evaluation.** **Conclusions:** **Considerable variability exists in the rates of positive screens and in polyp and adenoma detection rates among FSG examiners performing the procedures using a common protocol.**

Colorectal carcinoma is the second leading cause of cancer-related mortality in the United States.[1] Screening for colorectal cancer using fecal occult blood testing with follow-up colonoscopy has been shown to reduce colorectal cancer mortality and also to reduce colorectal cancer incidence by removing adenomas before they have a chance to progress to cancer.[2,3] Flexible sigmoidoscopy (FSG) detects both adenomas and early colorectal cancers in the distal colon and rectum and thus also potentially is capable of reducing colorectal cancer incidence and mortality. The efficacy of FSG in reducing colorectal cancer mortality currently is being evaluated in several large screening trials.[4–6] In addition, several case-control studies have shown that FSG is associated with reductions in colorectal cancer incidence and mortality.[7,8]

The performance characteristics of FSG are highly dependent on the examiner. Recently, the UK Flexible Sigmoidoscopy Screening Trial reported on variability among the examiners performing FSG examinations for that study.[9] They found large variations in polyp detection and adenoma detection rates across examiners. In this study, we analyzed the variability in FSG performance among examiners in the Prostate, Lung, Colorectal and Ovarian (PLCO) Cancer Screening Trial, a multicenter, ongoing, randomized trial evaluating, for the colorectal component, the effect of FSG screening on colorectal cancer mortality. We analyze here variability among examiners in the rates of positive and inadequate screens, as well as the rates of polyp and adenoma detection.

Methods

Randomization of men and women aged 55–74 years to the screened or usual care arm of the PLCO trial began in November of 1993 and was completed in July of 2001. The 10 PLCO centers were located in the following cities: Washington, DC, Pittsburgh, PA, Birmingham, AL, Detroit, MI, Marshfield, WI, Minneapolis, MN, St. Louis, MO, Denver, CO, Salt Lake City, UT, and Honolulu, HI, and enrolled a total of almost 155,000 patients. Patients in the screened arm received FSG at year 0 and year 5 (patients randomized before the middle of 1995 received FSG at year 3 instead of year 5). Men in the screened arm also received annual prostate-specific antigen tests, digital rectal examinations, and chest radiographs whereas women received annual cancer antigen 125

Abbreviations used in this paper: CI, confidence interval; CV, coefficient of variation; FSG, flexible sigmoidoscopy; GE, gastroenterologist; NP, nurse practitioner; OR, odds ratio; PLCO, Prostate, Lung, Colorectal and Ovarian Cancer Screening Trial.

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(CA-125) tests, transvaginal ultrasound examinations, and chest radiographs. A baseline questionnaire was administered around the time of randomization. The details of the design, conduct, and recruitment of the trial have been reported previously.[6] The study was approved by the institutional review boards of each study center. Eligibility criteria for the trial included no current treatment for cancer (except for basal or squamous cell skin cancer); no known prior cancer of the colorectum, prostate, lung, or ovaries; and, for patients randomized after April, 1995, no colonoscopy, sigmoidoscopy, or barium enema in the past 3 years.

An FSG examination was considered positive if the examiner noted a polypoid lesion or mass. The location, shape, and size (largest diameter) of each of the 4 largest lesions were recorded by the examiner. Lesions were not removed and did not undergo a biopsy examination. An FSG examination was considered inadequate if no lesion was found and the depth of insertion was less than 50 cm or less than 90% of the mucosa could be visualized. Patients were referred to their personal physicians for evaluation of screen-detected abnormalities. Information on diagnostic follow-up evaluation was collected using trained medical record abstractors who recorded the pathology, size, and location of each lesion found on endoscopy. We define a false-positive examination as a positive screening examination in which no distal polyp was found on endoscopic follow-up evaluation; in this article *distal* refers to the descending colon, sigmoid colon, and rectum. An adenoma that was 10 mm or greater in diameter, villous or tubulovillous, or had severe dysplasia was classified as advanced.

The PLCO protocol required that all FSG examiners be either physicians, registered nurses, nurse practitioners (NPs), or physician assistants. All examiners, except board-certified gastroenterologists or physicians with hospital privileges to perform FSG or colonoscopy, underwent training and certification by PLCO staff. Training and certification involved watching a videotape, observing 10 procedures and performing 10 practice procedures (ie, where one learns how to operate manual controls and withdraw the scope), and then performing as many successful training procedures under the guidance of a training gastroenterologist (a minimum of 25) as deemed necessary to show competence. Because the majority of PLCO examinations were performed by either gastroenterologists (GEs) or NPs, we limited the analysis to these groups. In addition, because there were a number of examiners who performed only a small number of examinations, we included in the analysis only results from examiners who performed at least 100 examinations. Only examinations from the baseline screening round were analyzed.

Statistical Methods

We were interested in estimating the true variability across FSG examiners in rates of screen positivity (and other outcomes). The observed variability in examiner positivity rates may not reflect true underlying variability because of several factors. First, because some examiners performed relatively few examinations there is some random error (noise) associated with the observed examiner rates that tends to make the observed variability an overestimate of the true underlying variability. Second, examiners in this study had a different mix of patients with respect to sex, age, and other factors that correlate with screen positivity; thus, some apparent variability in positivity rates could be caused by different subpopulations of patients for different examiners.

To deal with the earlier-described issues, we used a statistical tool known as mixed models.[10] Mixed models postulate that there are fixed effects that account for the effect of fixed patient or examiner covariates (such as age, sex, or smoking status) on the outcome of interest (eg, screen positivity) as well as random effects that account for the fact that one is sampling (in theory randomly) from a population of examiners and that each examiner in the population may have a different underlying rate of the outcome of interest. For each outcome of interest (positivity rate, inadequate rate), we first ran a full mixed model that incorporated random effects as well as fixed effects for patient age (4 age groups), sex, and smoking status (never, former, current), and examiner credential (NP vs GE). Note that inclusion of other patient covariates had little additional effect on estimates of variability. A backward stepwise procedure then was used to generate the final model. In addition to modeling positivity rates, we also modeled the rate of finding lesions of reported size (by the screening examiner) at least 10 mm in diameter, at least 5 mm in diameter, and at most 4 mm in diameter. The model details are given in Appendix 1. The coefficient of variation (CV) is defined here as the SD of the examiners' underlying rates divided by the mean of the examiners' underlying rates; it is multiplied by 100 and expressed as a percentage. In addition to calculating an overall CV across all examiners, CVs also were calculated separately for GEs and for NPs.

About 25% of positive-screen patients did not have endoscopic follow-up evaluation. We calculated the false-positive rate (false-positive screens over all positive screens) based only on positive screens with endoscopic follow-up evaluation. In addition, we calculated the distal polyp and distal adenoma detection rates by multiplying the proportion of screens that were positive by the proportion of positive screens with follow-up evaluation that had distal polyps or adenomas identified. A similar mixed model as described earlier was used to estimate variability in polyp and adenoma detection rates, and to estimate the correlation between screen-positive rates and false-positive rates (see Appendix 1).

Results

A total of 57,124 T0 FSG examinations were performed through June of 2000 by 158 different examiners. Table 1 shows the examinations performed by the 31 GEs and 33 NPs who performed at least 100 examinations. These 64 examiners at 10 clinical centers performed 49,955 examinations (87% of the total). The GEs came from 6 different screening centers and the NPs came from 8 different centers. Twelve NPs and 2 GEs

Table 1. FSG Examiners and Examinations

Number of examinations performed	Number of GE examiners (total examinations performed)	Number of NP examiners (total examinations performed)	Total number of examiners (examinations performed)
100–249	15 (2254)	6 (854)	21 (3108)
250–999	14 (7832)	15 (9428)	29 (17,260)
1000+	2 (3603)	12 (25,984)	14 (29,587)
Total	31 (13,689)	33 (36,266)	64 (49,995)

performed 1000 examinations or more. Of the study patients examined, 53% were men, 64% were aged 55–64 years (36% were aged 65–74 y), 10% were current smokers, and 43% were former smokers.

Table 2 shows the observed, mean, range, and SD of various characteristics of FSG performance for all examiners and for GEs and NPs separately; also shown are the CVs as estimated by the model. The mean observed examination positivity rate among all examiners was 26.7% (range, 9.3%–57.7%) with a modeled CV of 36%; a scatter plot of the individual examiner positivity rates is shown in Figure 1 (left plot). The model showed that male sex (odds ratio [OR], 1.7; 95% confidence interval [CI], 1.6–1.8), age (OR, 1.3 for 70- to 74-year-olds vs 55- to 59-year-olds; 95% CI, 1.2–1.4), and cigarette smoking (OR, 3.4 for current vs never smoker; 95% CI, 3.2–3.6) all were associated significantly ($P < .0001$) with the rate of positive examinations. The mean rate of positive examinations was not significantly different for GEs (mean, 25.1) compared with NPs (mean, 28.2). The CVs for detecting lesions of various reported sizes were larger than the overall CV described earlier. Estimated CVs were 44% and 52% for reporting at least 1 lesion of 10 mm or greater and 5 mm or greater, respectively (Table 2); individual examiner rates for lesions greater than 5 mm are shown in Figure 1 (middle plot). Although examiner credential was not associated significantly with reporting lesions of 5 mm or greater or 10 mm or greater, NPs had a significantly higher rate of reporting a maximum lesion size of less than 5 mm than did GEs (OR, 1.8; 95% CI, 1.5–2.2). Estimated CVs for reporting lesions of maximum size less than 5 mm were 71% for GEs and 53% for NPs, and 65% across all examiners. Note here that lesion size is as estimated by the screening examiner.

The false-positive rate for all examiners (defined as the percentage of positive examinations that were followed-up in which no distal polyps were found) averaged 35.5%, with a CV of 23%; no significant difference in means was found between GEs (mean, 36.9) and NPs (mean, 34.2). The (distal) polyp detection rate averaged 16.7% with a CV of 29% across all examiners (see Figure 1, right plot). CVs for (distal) adenoma and advanced adenoma detection across all examiners both were 21%. Figure 2 shows a scatter plot of examiners' observed positivity rate vs examiners' rate of false-positive examinations. The 2 rates are correlated positively, with a correlation coefficient of .70 ($P < .0001$). There was a similar significant correlation (of .82) between positivity rates and the rate of false-positive examinations when a false positive was defined in terms of failure to find a distal adenoma on follow-up evaluation as opposed to failure to find a distal polyp.

The mean examiner inadequate rate was 11.4% (range, 1%–27%); the estimated CV was 52% (Table 2). Older age (OR, 1.6 for 70- to 74-year-olds vs 55- to 59-year-olds; 95% CI, 1.5–1.7) and female sex (OR, 2.4; 95% CI, 2.2–2.6) significantly increased the risk for having an inadequate examination; no significant association with having an inadequate examination was observed for either patients' smoking status or examiner credential. The mean depth of insertion was similar for GEs (56.6 cm) as for NPs (54.2 cm); however, the difference was statistically significant. The CV for depth of insertion was quite low: 3.7%–5.0% (Table 2). Men had significantly longer average depths of insertion (57.1 cm) than women (53.3 cm), and younger patients had significantly longer average depths than older patients (55.9 cm for 55- to 59-year-olds vs 54.4 cm for 70- to 74-year-olds).

We also examined trends over time in FSG examiner performance. Specifically, for each examiner, we categorized each examination by whether it occurred temporally into the first, second, third, or last quarter of all examinations performed (by that examiner). By using the mixed model and controlling for patient age and sex, we found no significant trends by quarter in inadequate rates or in screen-positivity rates.

Discussion

We have examined variability in FSG performance among 64 examiners at 10 different centers who performed at least 100 examinations each and in totality performed almost 50,000 examinations for a cancer

Table 2. Mean and Variability of Examiner Rates

Finding	Observed examiner rates			Modeled CV (95% CI)[a]
	Mean	Range	SD	
Positive screen				
ALL	26.7	9–58	10.1	36 (30–40)
GE	25.1	10–53	9.5	35 (25–40)
NP	28.2	9–58	10.5	36 (26–41)
≥10-mm lesion				
ALL	3.4	0–9	1.9	44 (32–49)
GE	3.5	1–9	2.1	39 (24–52)
NP	3.4	0–9	1.9	40 (31–53)
≥5-mm lesion				
ALL	11.9	3–40	7.1	52 (43–57)
GE	13.4	4–32	7.4	51 (34–58)
NP	10.4	3–40	6.5	50 (35–58)
<5 mm lesion only				
ALL	14.8	0–40	8.9	65 (54–73)
GE	11.7	0–30	8.3	71 (54–85)
NP	17.8	2–40	8.4	53 (43–64)
Polyp detection rate				
ALL	16.7	7–36	5.3	29 (23–35)
GE	15.3	7–28	4.8	27 (20–34)
NP	18.0	7–36	5.4	27 (20–34)
False-positive rate[b]				
ALL	35.5	14–67	10.2	23 (17–27)
GE	36.9	14–58	10.2	23 (14–28)
NP	34.2	17–67	10.1	22 (14–27)
Adenoma detection rate				
ALL	10.0	4–15	2.5	21 (15–25)
GE	9.4	4–15	2.7	21 (13–27)
NP	10.6	6–15	2.3	21 (13–27)
Advanced adenoma detection rate[c]				
ALL	3.8	1–9	1.4	21 (15–25)
GE	3.7	1–9	1.7	21 (13–27)
NP	3.9	2–7	1.1	21 (13–27)
Inadequate rate				
ALL	11.4	1–27	5.5	52 (41–59)
GE	10.1	1–25	5.1	55 (40–66)
NP	12.7	2–27	5.6	47 (35–58)
Average depth of insertion (cm)				
ALL	55.4	50–63	2.7	4.4 (3.7–5.4)
GE	56.6	50–63	2.9	5.0 (4.0–6.8)
NP	54.2	50–58	1.9	3.7 (2.9–4.9)

NOTE. Adenoma and polyp detection rates are for distal lesions only.
ALL, all examiners.
[a] CV is SD over mean (× 100).
[b] Percent of positive examinations in which no distal polyp was found on follow-up evaluation.
[c] Large (≥10 mm), villous, or severely dysplastic (distal) adenomas.

screening trial. The CV across examiners was 36% for screen-positivity rate, 29% for polyp detection rate, and 21% for adenoma detection rate. The CVs reported here are similar to those found in other studies of screening FSG. Data from the ongoing UK sigmoidoscopy trial show observed CVs of 26% for polyp detection and 21% for adenoma detection among 13 FSG examiners each with 2400–3900 examinations performed.[9] In the Norwegian Colorectal Cancer Prevention Study of FSG, observed CVs were 19% for polyp detection and 17% for adenoma detection among 8 endoscopists each with 490–2246 examinations performed.[11]

The examiners in this study were located at 10 different screening centers. Because training and supervision in PLCO, although standardized, actually occurred at the individual screening centers, some of the variability observed across examiners cited here may be owing to a screening center effect. When screening center was added to the statistical model (as a fixed covariate), we found a statistically significant center effect on screen-positivity rates ($P = .002$). However, the center effect was responsible for only a small part of the observed variability in positivity rates. The model showed that the average CV of examiners at the same center would be 29%, compared with an overall CV for all examiners of 36%. Similarly, there was also a statistically significant center effect for inadequacy rate ($P < .0001$), with the average CV of examiners at the same center of 41%, compared with an overall CV of 52%. Some of the screening center effect presumably reflects the fact that local training and standards of practice serve to bring endoscopists at a center closer in line with each other. In addition, the population mix at each center may differ in terms of underlying risk factors for positive or inadequate examinations, over and above the ones controlled for in our analysis (ie, sex, age, and smoking status).

The CV of 44% for reporting a lesion of 10 mm or greater is greater than the overall CV for identification of any lesion (36%, Table 2). Because the reporting of a lesion of a given perceived size involves size estimation as well as lesion identification, any variability among examiners in how they estimate size would add to the overall CV for reporting 10 mm or greater lesions. Previous studies have shown variability in the estimation of polyp size.[12] However, the CV for reporting lesions of a given size increased as the size of the lesion decreased. Presumably, most of the variability for reporting large lesions arose because of variability in size estimation, although the variability in reporting small lesions was caused by both variability in size estimation and variability in detection rates. In addition, some examiners, even if they did detect a diminutive (1–2 mm) lesion, may not necessarily have reported such a finding if they did not think that it required any clinical follow-up evaluation.

NPs and GEs performed similarly in providing adequate examinations and in detecting polyps and adenomas, although NPs were more likely than GEs to identify small lesions (Table 2). Longer-term follow-up

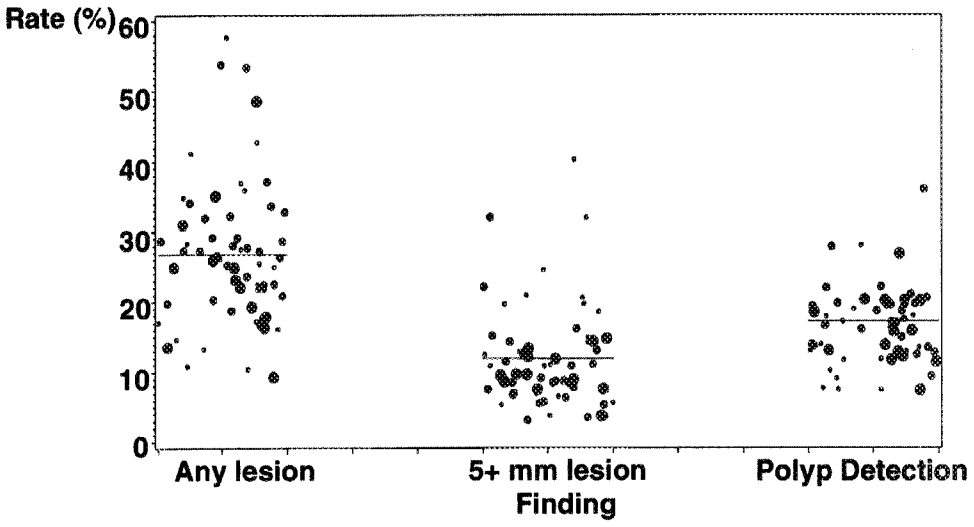

Figure 1. Scatter plot of observed individual examiner rates. Small, medium, and large circles represent examiners with 100–249, 250–999, and 1000+ examinations, respectively. Left plot shows screen positivity rate, middle plot shows rate of finding lesions 5+ mm in size, and right plot shows polyp detection rate. See text for details.

evaluation of patients may help determine whether the quality of examination was different between the 2 types of examiners, but the similar rates of detection and similar variability across examiners suggest that these 2 groups have a similar performance outcome for this screening protocol. It is not clear from these data, however, whether NPs and GEs also would have a similar performance outcome under a common type of FSG screening protocol that involves taking biopsy specimens of small lesions because examiners in PLCO did not perform biopsy examinations.

An important issue concerns the relationship between examiner variability and examination quality. Although high variability signifies a lack of uniformity across examiners, it is unclear whether it constitutes a lack of quality in some examiners. High variability may reflect subjective differences, with examiners operating at different points of a receiver-operator characteristic curve in terms of their threshold for false-positive vs false-negative results. Examiners with higher positivity rates tended to have higher rates of false-positive examinations. If these examiners were operating at a higher point on the receiver-operator characteristic curve, one also would expect that they would have correspondingly lower rates of false-negative examinations. We do not have the data to examine false-negative rates directly because patients with a negative FSG did not have immediate follow-up evaluation. However, one could examine this issue indirectly by determining whether patients seen at baseline by examiners with high positivity (and false-positive) rates have a lower incidence of adenoma or cancer at subsequent screening examinations than did patients seen by examiners with lower positivity rates. At the current time, there is not enough follow-up evaluation in PLCO to examine this question reliably; however, it is something we plan to examine in the future as more data accumulate. It also should be noted that some positive FSG examinations for which polyps are not found on subsequent colonoscopy actually may not be false-positive FSGs but in fact false-negative colonoscopies. Studies of tandem colonoscopy, or 1 colonoscopy immediately followed by a second, show that small polyps may be missed up to 27% of the time.[13,14]

From a clinical standpoint at this time, it is difficult to assess the significance of the observed variability in detection. Further follow-up data on subsequent events, as described earlier, may go some way in helping to be able to determine the clinical and public health impact of variability among examiners. An analysis of the relative benefit of higher vs lower positivity rates would have to

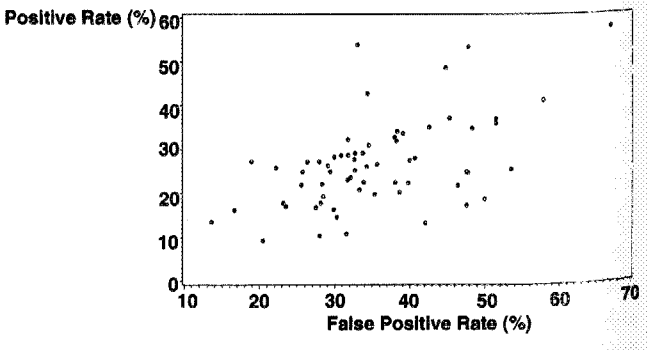

Figure 2. Scatter plot of examiner screen-positivity rate by examiner false-positive rate.

account for the price or cost of false positives, as well as the benefit of detecting adenomas. For example, it is possible that higher positivity rates, although reducing false-negative examinations, may increase evaluation with colonoscopy enough that it is not cost effective. The clinical trials of FSG, all of which implemented standardized training, indicate that training is unlikely to eliminate variability. Furthermore, it would be impossible to provide standardized training to all practitioners. Variability hardly is unique to sigmoidoscopy and is likely to be present in colonoscopy as well, as the tandem colonoscopy studies show. At this point we can recognize and understand that variability is present and substantial, and that further study of quality is essential to determining the optimal use of endoscopic techniques.

In estimating adenoma (or polyp) detection rates as the product of the probability of a positive screen and the probability, among those with follow-up evaluation, of detecting an adenoma given a positive screen, we implicitly are assuming that those with no follow-up evaluation (about 25%) are just as likely to have a distal adenoma (polyp) as patients with follow-up evaluation. In fact, this assumption probably is untrue because positive examinations with follow-up evaluation tended to have larger lesions detected at screening than positive examinations without follow-up evaluation, and larger lesions at screening are associated with an increased probability of finding an adenoma on follow-up evaluation. A more precise estimate could be derived by stratifying by lesion size (ie, by assuming that within each category of maximum lesion size at screening [<5, 5–9, 10+ mm], the probability of having a detectable adenoma [polyp] is the same regardless of follow-up status). This approach also could be used to refine the estimate of the false-positive rate. However, this would decrease the estimated adenoma and polyp detection rates by less than 5% and increase the false-positive rate by less than 5%. The change in estimates of variability would be expected to be of a similar or smaller magnitude.

Considerable variability exists in the rates of positive screens and in polyp and adenoma detection rates among FSG examiners. Because all of these examiners were trained in and attempted to follow the same study protocol, the amount of variability in general practice is likely to be greater than that observed here.

Appendix: Supplementary Data

Supplementary data associated with this article can be found in the online version at PII:S1542-3565(05)00286-7.

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